## REMARKS/ARGUMENTS

Reconsideration of this application is respectfully requested.

The undersigned wishes to express appreciation to the Examiner for granting the very constructive telephonic interview of December 20, 2010. The Examiner's record of January 3, 2011 adequately summarizes the interview and thus no further comment is believed to be necessary.

Claims 1, 4-12, 20 and 22 stand rejected under 35 USC 103 as allegedly being obvious over Neurath et al (EP 154902A, EP 448126A and USP 4,847,080), each in view of Zavaglia et al and Wei et al. Withdrawal of the rejections is submitted to be in order for the reasons that follow.

At the outset, the Examiner is reminded that the present invention relates to a method of determining whether an individual having HBV infection will respond to IFNα treatment. The method comprises analyzing a pre-treatment sample obtained from the individual for the presence or absence of antibodies reactive with a preS1 peptide consisting of the sequence of residues 94-117 (SEQ ID NO:1). The presence of such antibodies indicates that the individual is one who will respond to IFNα treatment. The absence of such antibodies indicates that the individual is one who will not respond.

The combination of Neurath et al in view of Zavaglia et al and Wei et al is deficient for the reasons detailed below and Applicants respectfully submit that one skilled in the art could not have arrived at the claimed method based on the combinations of teachings upon which the Examiner relies.

1. The combination of Neurath et al in view of Zavaglia et al and Wei et al provides no teaching or suggestion of a pre-treatment marker for HBV

Neurath et al and Zavaglia et al, taken alone or in combination, fail to provide any teaching or suggestion regarding pre-treatment markers for HBV. This deficiency is not remedied by Wei et al. Wei et al describes the detection of anti-preS1 (21-119aa) antibodies in HBV patients and suggests that the "presence of antibodies against preS1(21-119aa) region in serum during acute infection may indicate subsequent recovery".

The data set out in Wei et al, however, does not support the suggestion that the presence of preS1(21-119aa) antibodies is indicative of recovery.

*1.1 Wei shows no statistically significant association between anti-preS1(21-119) antibodies and acute HBV infection.*

Table 1 shows that, before recovery, 10 out of 16 acute hepatitis patients are anti-preS1(21-119) antibody positive (62.5%) and 6 out of 16 are negative (37.5%). After recovery, 9 out of 17 acute hepatitis patients are anti-preS1(21-119) antibody positive (52.9%) and 8 out of 17 are negative (47.1%).

Thus, contrary to the Examiner's assertion, this data shows no statistically significant difference between the presence and absence of the anti-preS1 antibodies in acute hepatitis B, either before or after recovery ($0.95<p<0.1$). The fact that antibodies are present in "more than half" of the patients is irrelevant since the difference in the numbers of patients with and without antibodies is too small to have any statistical significance. In the absence of a statistically significant association, anti-preS1 antibodies cannot even be said to be a marker for acute HBV infection.

Furthermore, regardless of the presence or absence of anti-preS1 (21-119) antibodies, all the patients with acute HBV infection recover. Since patients recover regardless of whether or not they have anti-preS1 (21-119) antibodies, the presence of anti-preS1 (21-119) antibodies has no value as a predictive marker for recovery from acute HBV infection. Because Wei et al provides no information about the presence or absence of anti-preS1 (21-119) antibodies in patients with acute HBV who fail to recover, the value as a predictive marker for recovery from acute HBV infection cannot be determined from the experiments described Wei et al.

Given the lack of any statistically significant association between anti-preS1 (21-119) antibodies and acute HBV infection, and the absence of any association whatsoever with recovery, Wei et al provides no teaching or suggestion which might have led one of skill in the art to reasonably expect that anti-preS1 antibodies could be used as a predictive marker for recovery from acute HBV infection.

*1.2 Wei shows no statistically significant association between anti-preS1(21-119) antibodies and chronic HBV infection*

The data in Table 1 also fail to support any statistically significant association between anti-preS1(21-119) antibodies and chronic HBV infection, still less any association with recovery from chronic HBV infection. Table 1 of Wei et al shows that 1 out of 30 healthy chronic hepatitis carriers is anti-preS1 antibody positive (3.3%) and 2 out of 29 chronic hepatitis patients are anti-preS1 antibody positive (6.9%). Given the very small proportion of chronic HBV patients or asymptomatic carriers who display the anti- preS1(21-119aa) reactivity, there can be no association between preS1(21-119aa) antibodies and chronic HBV.

*1.3 Wei shows no statistically significant association between the pretreatment presence of anti-preS1 (21-119) antibodies and recovery from chronic HBV infection*

On page 280 col 1, Wei et al describes a follow up study of chronic HBV patients. Ten chronic HBV inpatients were divided into two groups: one group was healthy chronic carriers who were seropositive HBeAg and high level of HBV-DNA and preS1 antigen. The other group was chronic HBV patients who had seropositive anti-HBe and low level of HBVDNA and preS1 antigen during the course of the disease.

During the follow-up period, no anti-preS1 (21-119aa) antibodies were found and no apparent improvement was observed in either group. In other words, regardless of whether or not the chronic carrier was healthy or had chronic hepatitis B, Wei et al fails to report anti-preS1 (21-119aa) reactivity in serum during follow-up in these two patient groups. Consequently, there is nothing in Wei et al which would have suggested that anti-preS1(21-119aa) antibodies could be used as a pre-treatment marker for recovery in these patients.

Wei et al report one patient who was different from the other chronic patients. This patient seroconverted from preS1 antigen to anti-preS1(21-119aa) antibodies after lamivudine treatment and this response correlated well with improvement in health. However, the anti-preS1(21-119aa) antibodies only appeared after elimination of HBV-DNA and declining levels of preS1 antigen. The patient had been followed three years before treatment with lamivudine was started and during this time no anti-preS1(21-119aa) antibodies were detected.

Since this seroconversion was reported in only a single patient, the relevance of this finding to the wider population of HBV patients cannot be determined from Wei et al. Thus, there is no teaching or suggestion by Wei et al that anti-preS1(21-119aa) antibodies could be used as a pre-treatment prognostic marker.

*1.4 The Wei et al data does not support prognostic use of anti-preS1 antibodies*

On page 280 of Wei et al, the authors suggest that the

> *anti-preS1 antibodies in serum may well be a new serological marker for clinical diagnosis of hepatitis B*

The appearance of anti-preS1(21-119aa) antibodies occurs, according to Wei et al, in about half of the patients in the course of acute hepatitis after the onset of the symptoms. As a serological marker for diagnosis, anti-preS1(21-119aa) antibodies would, therefore, only detect about half of patients with acute HBV infection.

Wei et al also claims that:

> *clinical follow-up results showed that appearance of anti-preS1 antibody in the course of most acute hepatitis patients could predict clearance of HBsAg and disappearance of preS1 dominants and HBV-DNA followed by elimination of HBsAg and seroconversion to anti-HBs*

This is simply not scientifically correct from the presented data. This claim is, in fact, directly contrary to the data, which shows that all acute patients recover, regardless of anti-preS1 antibodies.

It will be clear from the above that the combination of Neurath et al, Zavaglia et al and Wei et al would not have suggested any pre-treatment prognostic markers for HBV, much less pretreatment markers which might be predictive of IFN response in a patient.

2. The combination of Neurath et al in view of Zavaglia et al and Wei et al provides no teaching or suggestion of a pre-treatment marker predictive of IFN response.

Neurath et al provides no teaching or suggestion of IFN therapy for HBV markers.

Zavaglia et al teaches that IFNα can be used to treat chronic HBV patients. However, only 3 out of 18 patients responded to treatment after 12 months, while 4 more showed "delayed" responses. In other words, IFN treatment is only effective in a few cases. **There is no teaching or suggestion regarding the pre-treatment identification of patients who will respond to IFN treatment, nor even a suggestion that this might be possible**.

Wei et al is totally silent about IFN treatment or how it might relate to preS1 antibodies. As described above, Wei et al reports one patient who seroconverted from preS1 antigen to anti-preS1(21-119aa) antibodies after lamivudine treatment and this response apparently correlated well with improvement in health. However, even if this response in a single patient could be extrapolated to a larger population of HBV patients, response to lamivudine treatment cannot be equated with response to IFN treatment, and a patient responsive to one of these therapies may be totally unresponsive to another. Teachings relating to lamivudine treatment cannot, therefore, be extrapolated to IFN treatment, nor can post-treatment effects be extrapolated to pre-treatment.

This deficiency is not remedied by Neurath et al, which is also silent about IFN treatment, or Zavaglia et al, which is silent about preS1 antibodies and serves to highlight the problem addressed by the invention, i.e., **not all HBV patients are responsive to IFN treatment**.

The combination of Neurath et al in view of Zavaglia et al and Wei et al would not have provided any suggestion regarding a pre-treatment marker predictive of IFN responsiveness.

*2.1 Recovery is not the same as response to treatment*

The Examiner's assertion that the instant claims would have been obvious over the combination of Neurath et al, Zavaglia et al and Wei et al appears to result, at least partly, from

the view that acute HBV patients who recover naturally from the condition over time are by definition showing a response to IFN treatment which might have been administered to them. This view, however, is incorrect. A teaching of "recovery" cannot be equated with a teaching of "response to treatment" and a patient who "recovers" from HBV has not necessarily "responded" to treatment. For example, an individual with a common cold will recover eventually, regardless of what treatment has been administered. However, unless the treatment has had some effect on the severity or duration of the cold, the individual cannot be said to have "responded" to the treatment. Conversely, a patient with a terminal condition may respond to treatment, for example, by alleviating symptoms or increasing life expectancy, without recovering from the condition.

Given the Examiner's view, an acute HBV patient who will recover anyway, could be treated with snake oil (or anything else) and be said to have "responded" to it.

The instant claims relate to the identification of patients who will respond to IFNα treatment. This means that the IFNα treatment has a positive effect on the severity or duration of the HBV infection in the patient. Patients who display a positive reaction to IFNα treatment are "responders", whereas patients who do not display a positive reaction to IFNα treatment are "non-responders". Non-responders may include patients who recover from HBV but whose illness or recovery has not been positively affected by IFNα treatment. If the IFNα has no effect on the course of the recovery, then the individual has not responded to the treatment, even if they have recovered.

The fact that acute HBV patients who will eventually recover from the condition may be tested for preS1 antibodies according to Wei et al and/or may be treated with IFN according to Zavaglia et al does not amount to a teaching or suggestion that IFN treatment and preS1

antibodies are connected in any way or that the preS1 antibodies are predictive of whether or not the patient will respond to the IFN treatment. This deficiency is not remedied by Neurath et al.

The combination of Neurath et al, Zavaglia et al and Wei et al would, therefore, not have suggested the claimed invention.

3. The combination of Neurath et al in view of Zavaglia et al and Wei et al provides no teaching or suggestion of anti-preS1(94-117) antibodies as a predictive marker of IFN response.

The instant invention relates to the use of anti-preS1(94-117) antibodies as a predictive marker of IFN response.

Zavaglia et al is silent about pre-S1 antibodies, while Neurath et al teaches the detection of a range of preS1 antibodies and Wei et al teaches the detection of anti-preS1 (21-119aa) antibodies.

The Examiner contends that one skilled in the art could have arrived at the invention from the combination of Neurath et al, Zavaglia et al and Wei et al by simply epitope mapping the anti-preS1(21-119aa) antibodies of Wei et al. However, this reasoning assumes that the Wei et al antibodies were a single population and, further, that the antibodies detected by Wei et al were, in fact, anti-preS1 (94-117) antibodies. For the reasons set out below, both of these assumptions are unjustified.

Wei et al relates to antibodies which bind to the 98 amino acid preS1(21-119) protein. While it includes the preS1(94-117) epitope of the pending claims, the preS1(21-119) protein also contains numerous other epitopes (e.g., 27-35, 72-78, 32-47, 41-53, 94-105, 106-117, 21-30 and 29-48: see page 276 col 2). Antibodies that bind to any of these epitopes will bind to the preS1(21-119) protein and will be detected in the methods of Wei et al.

Furthermore, antibodies to numerous epitopes within the pre-S1(21-119) protein are present in individuals with HBV infections. This is shown, for example, by data set out in the specification. For example, Tables 2 and 3 (pages 31-34) show that preS1 (21-32) and preS1(32-47) are both present in HBV patients but are not predictive of IFN response. The population of anti-preS1(21-119aa) antibodies detected in Wei et al is, therefore, likely to be a mixture of antibodies which bind to the different epitopes within the preS1(21-119aa) sequence.

Epitope mapping would, therefore, fail to identify a single population of anti-preS1(94-117) antibodies but would simply identify a number of different sub-populations binding to different epitopes within the pre-S1(21-119) protein.

After epitope mapping, the skilled person would have been unable to establish whether any particular sub-population was predictive of recovery, given the data in Wei et al. Still less would the skilled person would have been able to associate any particular sub-set with IFNα responsiveness.

In order to arrive at the present invention, from Wei et al, the skilled person would firstly have to have been motivated to look for pretreatment markers for IFNα responsivenss. This motivation would not have been provided by Neurath et al, Zavaglia et al or Wei et al, taken alone or in combination. Even with this motivation, the skilled person would have needed to conduct an entire new research program to compare the presence of antibodies to different pre-S1 epitopes within the preS1(21-119aa) sequence with IFNα responsiveness in order to have arrived at the conclusion that only antibodies to a single one of these epitopes was predictive of response, whereas antibodies to the other epitopes, although present, were not predictive. This would have required considerable inventive insight as well as experimentation.

Put simply, the skilled person would not have found any teaching or guidance relating to the use of preS1(94 to 117) antibodies as a pre-treatment prognostic marker from the combination of Neurath et al, Zavaglia et al and Wei et al, still less any link between preS1(94 to 117) antibodies and responsiveness to IFNα treatment. The combination of Neurath et al in view of Zavaglia et al and Wei et al would not have suggested the association of preS1(94 to 117) antibodies (but not other preS1 antibodies) with a response to IFNα treatment.

In summary, the combination of Neurath et al, Zavaglia et al and Wei et al would not have suggested that antibodies reactive with the preS1 peptide (94 to 117) (SEQ ID NO:1) would be predictive of a response to IFNα therapy.

In view of the above, reconsideration and withdrawal of the rejections are requested.

This application is submitted to be in condition for allowance and a Notice to that effect is requested. Should the Examiner find that any issues remain outstanding, she is urged to contact the undersigned by phone to that every effort can be made to resolve them.

Respectfully submitted,

**NIXON & VANDERHYE P.C.**

By: /Mary J. Wilson/
Mary J. Wilson
Reg. No. 32,955

MJW:tat
901 North Glebe Road, 11th Floor
Arlington, VA 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100